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Serum zinc levels in patients with hirsutism

Zinc levels in hirsutism

Fehmi Unal, Berna Sermin Kılıc
Department of Obstetrics and Gynaecology, Istanbul Training and Research Hospital, Istanbul, Turkey

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Abstract
Aim : Hirsutism is the overgrowth of male-pattern terminal hair in women. Polycystic ovarian syndrome is the most detected endocrinopathy among women, and there are many reports of its association with metabolic syndrome. Zinc is the second most abundant trace element in the human body and integral part of many enzymes. There are several studies about serum zinc levels in polycystic ovarian syndrome, but zinc has not been adequately studied in idiopathic causes of hirsutism. Our study aims to investigate Zinc levels in hirsutism patients.
Material and Methods: This prospective case-control study involved 48 women with hirsutism. The hirsutism group consisted of 26 PCOS and 22 idiopathic hirsutism patients. Forty healthy, BMI and age-matched non-hirsute women were included as the control group.
Results: Statistically significant differences were found in Zn levels between non-hirsute and hirsute women (112.1 μg/dL versus 98.2 μg/dL, respectively), ($p < 0.001$). Total Cholesterol, LDL and AMH levels were also statistically significantly higher in hirsute patients.
Discussion: Our findings conclude that both idiopathic hirsutism and PCOS hirsutism patients have an increased metabolic syndrome risk. Both dyslipidemia and hyperandrogenemia contribute to the development of future metabolic syndrome. Low zinc levels in hirsute patients may provide insight into the pathogenesis of the disease, thus helping to reduce the risk of associated complications.

Keywords
Polycystic Ovary Syndrome, Zinc, Idiopathic Hirsutism

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Corresponding Author: Fehmi Unal, Department of Obstetrics and Gynaecology, Istanbul Teaching and Research Hospital, 34098, Istanbul, Turkey.
E-mail: unal.fehmi@gmail.com P: +90 212 459 60 00 F: +90 212 459 62 30
Corresponding Author ORCID ID: https://orcid.org/0000-0002-8182-2051
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Introduction

Hirsutism is the overgrowth of male-pattern terminal hair in women [1]. Hirsutism is detected in around 4-11% of women in the general population and it is the primary manifestation of hyperandrogenism in polycystic ovary syndrome (PCOS) [2]. Hyperandrogenaemia in females is mainly associated with PCOS, and there are many reports of its involvement with metabolic syndrome (MetS) [3,4]. Increased adipokines, chemokines, and interleukins and decreased adiponectin levels point to the inflammation in PCOS [3]. There are studies evaluating the releation of hirsutism and metabolic disorders in PCOS patients [5]. Hyperandrogenaemia components have been mainly found to be potent predictors of metabolic disorders in many studies [6].

Another frequent cause of hirsutism worldwide is idiopathic hirsutism (IH) [1]. In a recent study, a link between obesity, dyslipidemia, and insulin resistance with IH was found [7]. Studies that evaluate the association of MetS and insulin resistance in IH patients have conflicting results [8,9].

The most important essential and second most abundant trace element in the body is zinc (Zn). Zn is an integral part of over 300 enzymes involved in the function and structure of those enzymes [10]. Through these enzymes, Zn is released in a large variety of metabolic processes involving lipids, nucleic acid synthesis or degradation, and protein and carbohydrate metabolism. In addition to diabetes [11], Zn deficiency is linked to cardiovascular disease (CVD) and atherogenesis in many studies [12].

Although there are conflicting results regarding the serum Zn levels in PCOS patients [13], less information is present about the Zn levels in idiopathic hirsutism. This study aims to evaluate metabolic syndrome markers and Zn levels in hirsutism patients with or without PCOS, and age and BMI-matched controls.

Material and Methods

Study population

This prospective case-control study was performed between January 2020 and January 2021. Forty-eight consecutive patients who admitted with hirsutism symptoms to our outpatient clinic of the Department of Obstetrics and Gynaecology, Istanbul Training and Research Hospital were recruited. The hirsutism group was of reproductive age and consisted of two groups: 26 had PCOS and 22 had IH. PCOS was diagnosed in the presence of 2 out of 3 Rotterdam 2013 criteria (clinical/ biochemical signs of hyperandrogenism, oligo- anovulation, or ultrasound findings of polycystic ovaries) [14] with the exclusion of congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, severe hyperprolactinemia and androgen-secreting tumors. All 26 of our PCOS patients met the hirsutism criteria of biochemical /clinical signs of hyperandrogenism using the modified Ferriman-Gallwey (mFG) method [15]. Biochemical hyperandrogenism was defined as an elevation of the total testosterone (TT) and/or dehydroepiandrosterone sulfate (DHEA-S) levels above normal adult female levels (levels of TT (normal range: 10–74 ng/dL) and/or DHEA-S (normal range: 18–391 µg/dL) [14]. The clinical hirsutism group consisted of patients with an mFG score of 8 and above. IH was defined as hirsutism (mFGS ≥8) with normal menstrual cycles (25 to 35 days) and normal serum androgen profile levels (TT and DHEA-S), which were defined according to the reference values of commercial kits and normal ovaries by sonography without any other signs of virilization [15,16].

The control group consisted of 40 healthy, premenopausal women who voluntarily participated in our study and were admitted to our outpatient clinic for routine gynecological examination. The control group and hirsutism patients were matched for BMI and age. All controls were examined prior to enrollment, all had regular menses, and had no hyperandrogenism or signs of hirsutism (mFGS<8).

Women taking contraceptive pills, antiandrogens, or glucocorticoids were excluded from the study.

Samples were collected following a consent form (approved by the Local Ethical Committee date: 20.12.2019, acceptance number: 2114) obtained from all studied cases and controls. The clinical investigations were carried out according to the Declaration of Helsinki.

Biochemical and hormonal tests

Morning venous blood samples were obtained between 9 and 10 am between days 3 and 5 of the menstrual cycle; after centrifugation at 2000-3000 rpm at 4°C for 20 minutes, serum samples were separated and frozen at -80°C until analysis. Fasting plasma glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride levels were measured using spectrophotometric analyses on a Beckman Coulter AU 5800 (Beckman Coulter, Brea, analyzers (Abbott Diagnostics, US)). Follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), DHEAS, TT and serum levels of thyroid-stimulating hormone (TSH) were measured immunoenzymatically. An automated electrochemiluminescence immunoassay (ECLIA) and Roche-Cobas E411 (Roche Diagnostics, Mannheim, Germany) were used to determine serum anti-Mullerian hormone (AMH) concentrations.

Determination of Zinc

Serum Zn concentrations were measured with a commercial Rel Assay zinc measurement kit (Gaziantep, Turkey) using a fully automated photometric method (Abbott ARCHITECT c8000 clinical chemical analyzer). The principle of the Zn2+ method is that the total zinc in the sample changes to light pink from the red-orange color of 5-Br-PAPS under alkaline conditions. The concentration of Zn2+ in the sample (µg/dL) is proportional to the absorbance change measured at 548 nm. The standard of the method is zinc sulfate.

Statistical method

The Shapiro-Wilk Francia test was used to determine the suitability of univariate data to the normal distribution, while variance homogeneity was evaluated with the Levene test. Bootstrapping was used together with independent samples t-test results, while the Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups according to quantitative data. Kendall's tau-b test was used to examine the correlations of quantitative variables with each other Quantitative variables are presented in the tables as the mean ± SD (standard deviation) and median (minimum/ maximum), while categorical variables are expressed as n (%). The variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The main characteristics of the two groups are listed in Table 1. In the demographic data, statistically significant differences between the tested groups were found for Zn levels 98.2 (88.7/108.4) μg/dL vs. 112.1 (105.7 /124.8), (p < 0.001), total cholesterol 184 (155 / 200) vs. 150 (142/150) mg/dL, (p < 0.001), LDL 120 (94 / 138) vs. 81 (77 / 95) mg/dL, (p< 0.001), AMH 4.7 (2.4 / 9.1) vs. 2.25 (0.9/4.1) ng/ml, (p = 0.001), FSH 7 (5.9 / 8.44) vs. 7.8 (6.75/11.2) mIU/mL, (p< 0.001), (hirsutism vs non-hirsutism, respectively) (Table 1).

Table 1. Biochemical and demographic characteristics of Hirsutism and Non-Hirsutism patients

	Non-Hirsutism (n=40)	Hirsutism (n=48)	P
Age (years), median (q1/q3)	29 (22/37)	28 (27/33)	0.219
BMI (Kg/m2), mean (SD.)	24.37 (3.37)	25.57 (4.82)	0.362
	median (q1/q3)	median (q1/q3)	
Zinc (μg/dL)	112.1 (105.7/124.8)	98.2 (88.7/108.4)	<0.001ᵘ
T. cholesterol (mg/dL)	150 (142/150)	184 (155/200)	<0.001ᵘ
Triglyceride (mg/dL)	80 (70/117)	86 (66/103)	0.905ᵘ
HDL (mg/dL)	42 (41/44)	45.5 (39/58)	0.258ᵘ
LDL (mg/dL)	81 (77/95)	120 (94/138)	<0.001ᵘ
HgA1C	5.2 (5/5.5)	5.3 (5.1/5.6)	0.340ᵘ
T. Testosterone (ng/dL)	40 (35/45)	42.15 (35/61.5)	0.209ᵘ
DHEA-SO4 (μg/dL)	130.25 (80/236)	135 (90/135)	0.819ᵘ
AMH (ng/ml)	2.25 (0.9/4.1)	4.7 (2.4/9.1)	0.001ᵘ
FSH (mIU/mL)	7.8 (6.75/11.2)	7 (5.9/8.44)	0.019ᵘ
LH (mIU/mL)	6 (5/8)	5.735 (3.8/8.6)	0.832ᵘ
E2 (pg/mL)	47 (13/66)	32.5 (28.925/38.5)	0.679ᵘ
PRL (μg/L)	12.5 (9/16)	12.5 (8.8/22)	0.480ᵘ
TSH (ng/ml)	1.6 (0.9/2.4)	1.6 (1/2.69)	0.678ᵘ
Fasting Glucose (mg/dL)	90 (85/96)	87 (82/94)	0.302ᵘ

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, DHEA-SO4: Dehydroepiandrosterone sulfate, AMH: Anti-mullerian hormone, FSH: Follicle-stimulating hormone LH: Luteinizing hormone, E2: Estradiol, PRL Prolactin:, TSH: Thyroid-stimulating hormone

Table 2. Correlation of Zn concentrations with the hormonal and metabolic parameters in hirsutism patients

	Zinc (μg/dL)	
	r	p
Age (years)	-0.135	0.069
BMI (kg/m2)	0.152	0.057
Total cholesterol (mg/dL)	0.213	0.011
Triglyceride (mg/dL)	0.060	0.561
HDL (mg/dL)	0.138	0.184
LDL (mg/dL)	0.256	0.002
HgA1C	0.086	0.435
Total Testosterone (ng/dL)	0.049	0.565
DHEA-SO4 (μg/dL)	0.204	0.012
AMH (ng/ml)	0.123	0.104
FSH (mIU/mL)	-0.004	0.959
LH (mIU/mL)	0.114	0.191
E2 (pg/mL)	-0.425	0.008
PRL (μg/L)	0.127	0.107
TSH (ng/ml)	0.005	0.947
Fasting glucose (mg/dL)	0.067	0.417

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, DHEA-SO4: Dehydroepiandrosterone sulfate, AMH: Anti-mullerian hormone, FSH: Follicle-stimulating hormone LH: Luteinizing hormone, E2: Estradiol, PRL Prolactin:, TSH: Thyroid-stimulating hormone

There was no difference between the PCOS hirsutism and idiopathic hirsutism groups in terms of Zn levels (115.9 μg/dL vs. 109.9 μg/dL) (p=0,364).

Correlations of metabolic parameters with Zn levels were found between total cholesterol for Zn (r = 0,213, p = 0,011), LDL for Zn (r = 0.256, p = 0.002), DHEA-SO4 for Zn (r 0.204, p=0.012) and E2 for Zn (r -0.425, p=0.008), (Table 2). No correlations were found between Zn levels with age, BMI, triglyceride, HDL, HgA1C, AMH and fasting glucose levels in hirsutism patients.

Discussion

In our study, multiple hormonal and metabolic parameters were investigated. Zn levels were lower in the hirsutism group. In addition, the relationship between zinc and plasma LDL and total cholesterol levels may suggest that increased dyslipoproteinemia contributes to increased MetS risk in hirsutism patients.

Low Zn intake with diet and low plasma levels of Zn have been associated with an increased prevalence of Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and hypertension [17]. In a recent cross-sectional study with 911 Chinese children, although the Zn concentration was in the normal range, the risk of elevated triglycerides was positively associated with tertiles of Zn [18]. In a recent systematic review and meta-analysis of 10 studies, an increased prevalence of coronary artery disease was associated with low serum Zn levels [19]. Our study supports those findings, as we found a correlation of Zn levels with total cholesterol and LDL in hirsutism patients, which are important risk factors for CVD.

Only one study investigated Zn levels in PCOS and IH, and the mean Zn levels in adolescents with hirsutism and the control group were similar. Additionally, hirsutism subgroup analysis showed no difference in mean Zn levels between IH and PCOS, and they hypothesized that mild hirsutism in adolescents was not associated with hyperandrogenaemia [20]. We found low Zn levels in hirsutism patients regardless of whether they had PCOS or IH; we assume that long-term complications such as cardiovascular disease and/or T2DM may arise in those patients if not managed effectively. Early intervention should be offered to those patients to provide early targeted preventive treatment. We conclude that the adverse effects of hirsutism on metabolic parameters may be based on time and duration.

Another interesting finding was a correlation of Zn levels with DHEA-SO4 levels in hirsutism patients. Hitherto, studies have focused on the effects of supplementation on testosterone levels [21]. The correlation of Zn levels with androgen hormone levels has not been investigated enough. Jamilian et al. evaluated the effects of Zn supplementation on endocrine outcomes in PCOS patients and found beneficial effects on hirsutism but no effect on hormonal profiles [22]. Zn inhibits 5-alpha reductase and decreases the production of dihydrotestosterone, mainly acting on peripheral tissues [20]. Zn is also involved in gonadal hormone synthesis and gonadal androgen hormone and receptor metabolism [23], but little is known about its role in hyperandrogenism. Therefore, we hypothesized that zinc deficiency may have causal link with the severity of hirsutism not only in PCOS but also in IH patients, and the probability of Zn deficiency as a causal and/or prognostic factor of hirsutism was demonstrated.

It is also important to consider a therapeutic approach to hirsutism patients apart from hair removal methods and/or oral contraceptive or anti-androgen medications for cosmetic reasons. Considering the long-term management of hirsutism associated with underlying metabolic conditions is necessary for medical professionals. Several studies have confirmed that the relative failure of dietary treatment and counseling leads to disappointing results [24]. In a meta-analysis, Ruz M et al. [25] found that the results of observational and cross-sectional studies on the plausible relationship between serum Zn levels and the incidence of MetS are inconsistent. Four out of ten trials that included Zn supplements as a treatment for MetS had positive results with Zn supplementation in glycemic control parameters, reduction of oxidative stress and lipid profile improvement.

Hirsutism is a non-life-threatening endocrine disorder with long-term health repercussions, such as cardiovascular and metabolic disturbances, and a negative influence on psychological well-being.

The small sample size of enrolled IH patients in our study appears to be the main limitation. The second limitation may be the lack of long-term health information about the patients. The strength of our study is that this is one of the first studies evaluating the relationship between hirsutism and Zn. As far as we know, only one study has evaluated the levels of Zn in IH.

Conclusion

Both IH and PCOS hirsutism patients have an increased risk of MetS; dyslipidemia and hyperandrogenemia contribute to the development of future CVD and T2DM risk. Several mechanisms involved in Zn action suggest the potential roles of Zn in the treatment of IH and PCOS hirsutism.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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